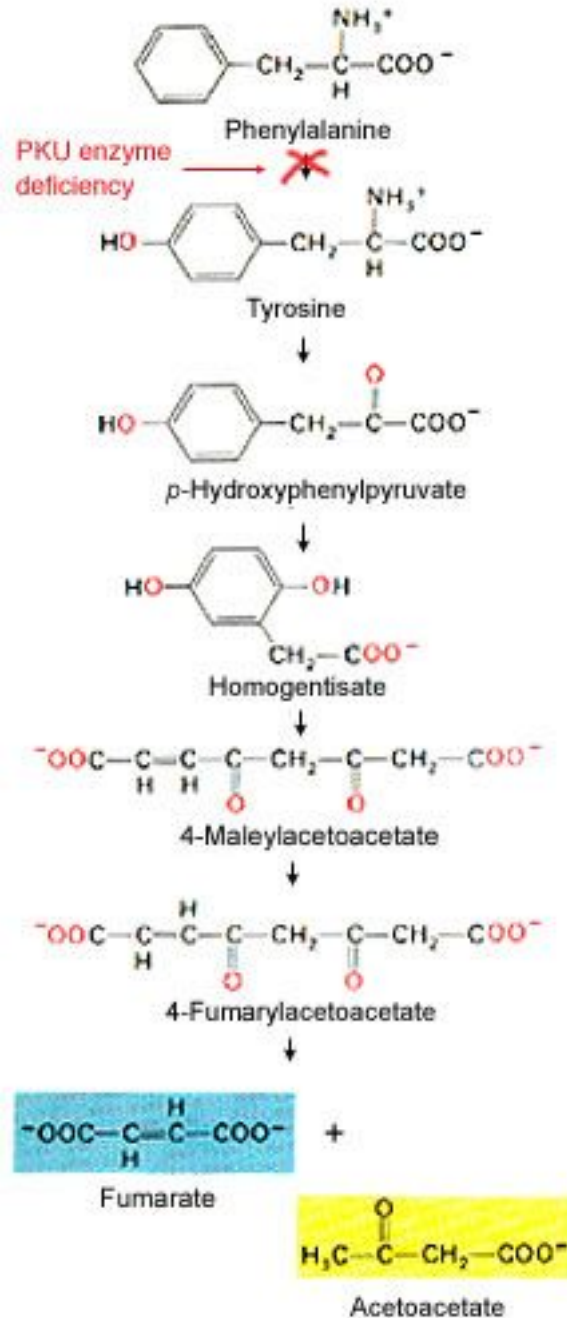


Nutritional and Metabolic Diseases



Surplus amino acids are broken down to make metabolic energy. The first step in the degradation pathway of phenylalanine and tyrosine requires the enzyme phenylalanine hydroxylase. Individuals lacking this enzyme suffer from phenylketonuria (PKU), an inborn error of metabolism. [Modified from Stryer, L. (1988) Biochemistry 3rd edn, W.H. Freeman and Co., with permission.]

Metabolism is the means by which the body derives energy and synthesizes the other molecules it needs from the fats, carbohydrates and proteins we eat as food, by enzymatic reactions helped by minerals and vitamins.

This global statement masks the complicated network of enzyme- catalyzed reactions that occurs in cells. Although this page is devoted to diseases caused by errors in metabolic processes, there is actually a significant level of tolerance of errors in the system: often, a mutation in one enzyme does not mean that the individual will suffer from a disease. A number of different enzymes may compete to modify the same molecule, and there may be more than one way to achieve the same end result for a variety of metabolic intermediates. Disease will only occur if a critical enzyme is disabled, or if a control mechanism for a metabolic pathway is affected.

Here, we highlight the diseases of metabolism for which a gene has been identified, cloned and mapped. Many of these are inborn errors of metabolism: inherited traits that are due to a mutation in a metabolic enzyme; others involve mutations in regulatory proteins and in transport mechanisms.

Adrenoleukodystrophy

Adrenoleukodystrophy (ALD) is a rare, inherited metabolic disorder that afflicts the young boy Lorenzo Odone, whose story is told in the 1993 film "Lorenzo's oil." In this disease, the fatty covering (myelin sheath) on nerve fibers in the brain is lost, and the adrenal gland degenerates, leading to progressive neurological disability and death.

People with ALD accumulate high levels of saturated, very long chain fatty acids in their brain and adrenal cortex because the fatty acids are not broken down by an enzyme in the normal manner. So, when the *ALD* gene was discovered in 1993, it was a surprise that the corresponding protein was in fact a member of a family of transporter proteins, not an enzyme. It is still a mystery as to how the transporter affects the function the fatty acid enzyme and, for that matter, how high levels of very long chain fatty acids cause the loss of myelin on nerve fibers.

More recently, all the transporters related to ALD protein have been found in the yeast *Saccharomyces cerevisiae*, and a mouse model for the human disease has been developed. These and

other molecular biology approaches should further our understanding of ALD and hasten our progress toward effective therapies.



Myelin-stained section of brain in adrenoleukodystrophy, showing build-up of long-chain fatty acids [With thanks to Kevin Roth and Robert Schmidt, Washington University, St. Louis, MO, USA, for supplying the image.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=ALD] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?l=215] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=7262393&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=Adrenoleukodystrophy%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=Adrenoleukodystrophy] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=300100] catalog of human genes and disorders

Websites

Fact sheet [www.ninds.nih.gov/health_and_medical/disorders/adrenolu_doc.htm] from The National Institute of Neurological Disorders and Stroke, NIH

GeneClinics [www.geneclinics.org/profiles/x-ald/] a medical genetics resource

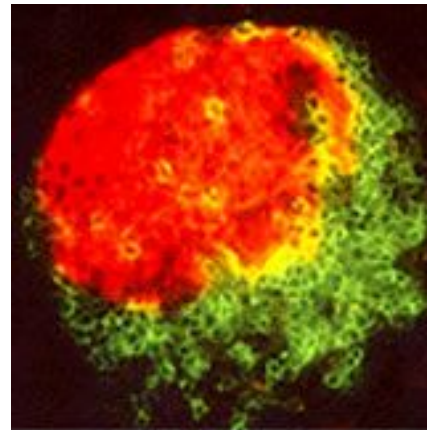
Diabetes, Type 1

Diabetes is a chronic metabolic disorder that adversely affects the body's ability to manufacture and use insulin, a hormone necessary for the conversion of food into energy. The disease greatly increases the risk of blindness, heart disease, kidney failure, neurological disease, and other conditions for the approximately 16 million Americans who are affected by it. Type 1, or juvenile onset diabetes, is the more severe form of the illness.

Type 1 diabetes is what is known as a 'complex trait', which means that mutations in several genes likely contribute to the disease. For example, it is now known that the insulin-dependent diabetes mellitus (IDDM1) locus on chromosome 6 may harbor at least one susceptibility gene for Type 1 diabetes. Exactly how a mutation at this locus adds to patient risk is not clear, although a gene maps to the region of chromosome 6 that also has genes for antigens (the molecules that normally tell the immune system not to attack itself). In Type 1 diabetes, the body's immune system mounts an immunological assault on its own insulin and the pancreatic cells that manufacture it. However, the mechanism of how this happens is not yet understood.

About 10 loci in the human genome have now been found that seem to confer susceptibility to Type 1 diabetes. Among these are 1) a gene at the locus IDDM2 on chromosome 11 and 2) the gene for glucokinase (GCK), an enzyme that is key to glucose metabolism which helps modulate insulin secretion, on chromosome 7.

Conscientious patient care and daily insulin dosages can keep patients comparatively healthy. But in order to prevent the immunoresponses that often cause diabetes, we will need to experiment further with mouse models of the disease and advance our understanding of how genes on other chromosomes might add to a patient's risk of diabetes.



T lymphocytes attacking insulin-producing pancreatic islet cells. [Image credit: A. Cooke and John Todd, Wellcome Trust Center for Human Genetics, Oxford, UK.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=diabetes+NOT+morbidity] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=diabetes&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4503951&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=diabetes%20AND%20pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=diabetes] online books section

OMIM [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=omim&details_term=diabetes] catalog of human genes and disorders

Websites

Patient information on diabetes [www.niddk.nih.gov/health/diabetes/diabetes.htm] from the National Institute of Diabetes and Digestive and Kidney Diseases, NIH

Juvenile Diabetes Foundation [www.jdfcure.com] 'creating a world without diabetes'

American Diabetes Association [www.diabetes.org/default.htm] research and information

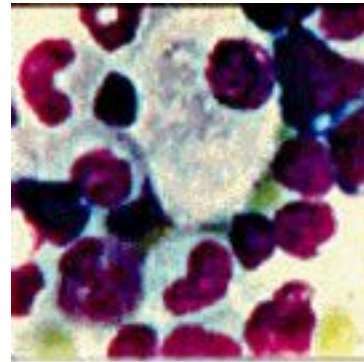
Gaucher Disease

Gaucher (pronounced "go-SHAY") disease is an inherited illness caused by a gene mutation. Normally, this gene is responsible for an enzyme called glucocerebrosidase that the body needs to break down a particular kind of fat called glucocerebroside. In people with Gaucher disease, the body is not able to properly produce this enzyme, and the fat can not be broken down. It then accumulates, mostly in the liver, spleen, and bone marrow. Gaucher disease can result in pain, fatigue, jaundice, bone damage, anemia, and even death.

Gaucher disease is considerably more common in the descendants of Jewish people from Eastern Europe (Ashkenazi), although individuals from any ethnic group may be affected. Among the Ashkenazi Jewish population, Gaucher disease is the most common genetic disorder, with an incidence of approximately 1 in 450 persons. In the general public, Gaucher disease affects approximately 1 in 100,000 persons. According to the National Gaucher Foundation, 2500 Americans suffer from Gaucher disease.

In 1991, enzyme replacement therapy became available as the first effective treatment for Gaucher disease. The treatment consists of a modified form

of the glucocerebrosidase enzyme given intravenously. Performed on an outpatient basis, the treatment takes about 1–2 h and is given every 2 weeks. Enzyme replacement therapy can stop and often reverse the symptoms of Gaucher disease, allowing patients to enjoy a better quality of life.



Gaucher cells. [Image credit: E. Beutler, Scripps Research Institute, La Jolla, CA, USA.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=Gaucher] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=Gaucher&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4503935&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=%28Gaucher%5BText%20Word%5D%20AND%20%22pubmed%20pmc%22%5BFilter%5D%29] online full text

Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=Gaucher] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=230800] catalog of human genes and disorders

Websites

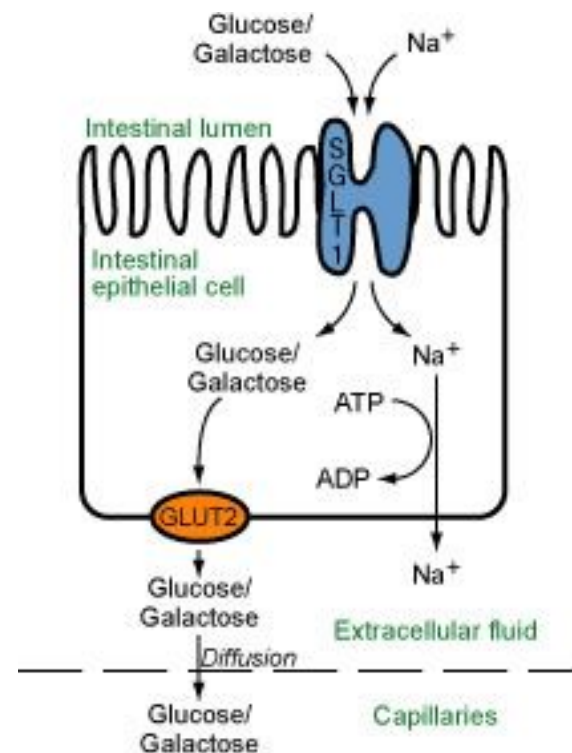
National Gaucher Foundation [neuro-www2.mgh.harvard.edu/gaucher/ngfusa.html] supporting research into the causes of Gaucher disease

Glucose Galactose Malabsorption

Glucose Galactose Malabsorption (GGM) is a rare metabolic disorder caused by a defect in glucose and galactose transport across the intestinal lining. GGM is characterized by severe diarrhea and dehydration as early as the first day of life and can result in rapid death if lactose (milk sugar), sucrose (table sugar), glucose, and galactose are not removed from the diet. Half of the 200 severe GGM cases found worldwide result from familial intermarriage. At least 10% of the general population has glucose intolerance, however, and it is possible that these people may have milder forms of the disease.

GGM is an autosomal recessive disorder in which affected individuals inherit two defective copies of the *SGLT1* gene, located on chromosome 22. Normally within the space enclosed by the small intestine (called the lumen), lactose is broken down into glucose and galactose by an enzyme called lactase, while sucrose is broken down into glucose and fructose by an enzyme called sucrase. The protein product of *SGLT1* then moves the glucose and the galactose from the lumen of the small intestine into intestinal cells. Usually the mutations carried by GGM individuals result in nonfunctional truncated SGLT1 proteins or in the improper placement of the proteins such that they can not transport glucose and galactose out of the intestinal lumen. The glucose and galactose, if left untransported, draw water out of the body into the intestinal lumen, resulting in diarrhea.

Although no cure exists for GGM, patients can control their symptoms (diarrhea) by removing lactose, sucrose, and glucose from their diets. Infants showing a prenatal diagnosis of GGM will thrive on a fructose-based replacement formula and will later continue their "normal" physical development on a fructose-based solid diet. Older children and adults with severe GGM can also manage their symptoms on a fructose-based diet and may show improved glucose tolerance and even clinical remission as they age.



Co-transport of sodium and glucose or galactose by SGLT1. For every two sodium ions SGLT1 moves inside the cell down the sodium concentration gradient, one glucose or galactose molecule moves with it. The glucose/galactose is then transported into the extracellular fluid by GLUT2, and diffuses into the capillaries. Sodium is actively transported out of the cell into the intercellular space so as to maintain the intracellular sodium concentration gradient.

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=SGLT1] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=SGLT1&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=5730021&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=SGLT1%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=SGLT1] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=182380] catalog of human genes and disorders

Websites

National Organization For Rare Disorders [www.stepstn.com/cgi-win/nord.exe?proc=Redirect&type=rdb_sum&id=749.htm] nonprofit organization

National Digestive Diseases Information Clearinghouse [www.niddk.nih.gov/health/digest/nddic.htm] from the National Institute of Diabetes and Digestive and Kidney Diseases, NIH

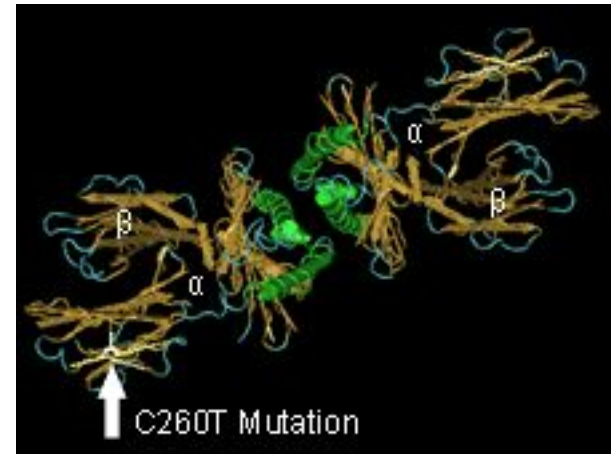
Hereditary Hemochromatosis

Hereditary hemochromatosis is an inherited disorder that increases the amount of iron that the body absorbs from the gut. Symptoms are caused by this excess iron being deposited in multiple organs of the body. Most commonly, excess iron in the liver causes cirrhosis, which may develop into liver cancer. Iron deposits in the pancreas can result in diabetes. Similarly, excess iron stores can cause cardiomyopathy, pigmentation of the skin, and arthritis.

Many mutations in the body's iron transport system can cause hemochromatosis, however most cases are caused by mutations in the *HFE* gene located on chromosome 6. A missense mutation leads to a substitution of a tyrosine residue in place of a cysteine residue at position 260 (C260Y, formerly called C282Y) in the HFE protein. This is thought to affect how the HFE protein interacts with the transferrin receptor (TFR1), which plays an important role in iron homeostasis. A less common mutation, H63D, has also been identified in the *HFE* gene.

Hemochromatosis is one of the most common autosomal recessive disorders among Caucasians in the United States; however only a small proportion of these people suffer any symptoms. This may be attributable to both environmental (diet and blood loss) and genetic factors. Recent advances in

developing animal models that show the complications of hemochromatosis may soon provide useful tools in deciphering how other genes play a part in iron regulation.



HFE protein is similar in structure to MHC Class I, consisting of two pairs of alpha and beta chains. The mutation occurs in the alpha 3 domain and disrupts the association between the chains. Mutant HFE is unable to bind to the iron-loaded transferrin receptor. Without this interaction, the receptor brings more iron into cells.

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=hemochromatosis] see gene locations
 LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=hemochromatosis&ORG=Hs&V=0] collection of gene-related information
 Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=15485419&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=hemochromatosis%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text
 Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=hemochromatosis] online books section
 OMIM [www.ncbi.nlm.nih.gov/entrez/dispmim.cgi?id=235200] catalog of human genes and disorders

Websites

Hemochromatosis [www.niddk.nih.gov/health/digest/pubs/hemochrom/hemochromatosis.htm#info/] from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Health
 American Hemochromatosis Society [www.americanhs.org/] information and patient support
 Factsheet [www.cdc.gov/nccddp/dnpa/hemochromatosis/] from the Centers for Disease Control and Prevention
 GeneReviews [www.genetests.org/profiles/hemochromatosis/] a medical genetics resource

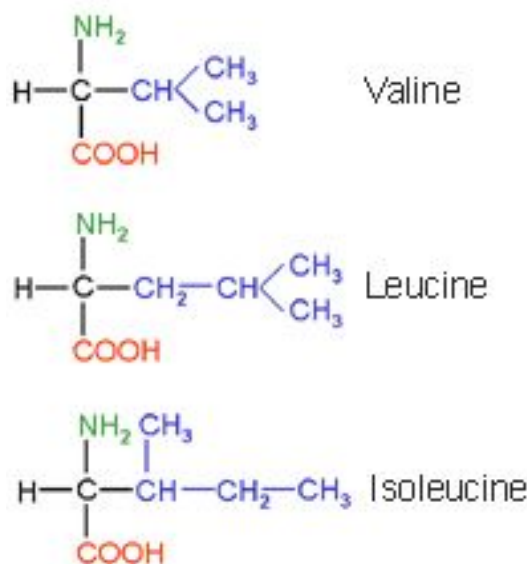
Maple Syrup Urine Disease

Maple Syrup Urine Disease (MSUD) is an inherited disorder so named because one of its first signs is urine that has an odor reminiscent of maple syrup. The underlying defect disrupts the metabolism of certain amino acids. These are amino acids that have a branched side chain. Because they cannot be fully broken down, they accumulate in the urine, along with their metabolites (alpha-ketoacids) to give the distinctive smell. Left untreated, there is progressive neurodegeneration leading to death within the first months of life.

Three amino acids have branched side chains: valine, leucine, and isoleucine. They are an essential element in the diet and are broken down by the body to yield energy. One step in this breakdown involves the branched-chain alpha-ketoacid dehydrogenase (BCKDH) complex, which consists of three catalytic components and two regulatory enzymes. In total, six loci encode for the BCKDH, and mutations in different loci are responsible for the genetic variety seen in MSUD.

The Mennonite community of Lancaster County, Pennsylvania is particularly afflicted by MSUD, with over 1 of 176 individuals affected. This is due to a high carrier rate of a mutation in the E1alpha-subunit of the BCKDH complex. By contrast, the disease is rare in the general population.

Currently treatment consists of restricting the dietary intake of branched-chain amino acids to the absolute minimum that is needed for growth. However, studies have already shown that it is possible to transfer subunits of the BCKDH enzyme into cells using a retrovirus. Similar advances in gene therapy may provide a future cure.



Amino acids contain an alpha carbon (C), an amino group (NH₂), a carboxyl group (COOH), and a unique side group (R).

All branched-chain amino acids have side groups that contain a branched carbon chain.

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=maple+syrup+urine+disease] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=maple+syrup+urine+disease&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=548403&org=1] related sequences in different organisms

The literature

Research articles [http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=maple+syrup+urine+disease%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=maple+syrup+urine+disease] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispmim.cgi?id=248600] catalog of human genes and disorders

Websites

MSUD Family Support Group [www.msud-support.org/] patient information and support

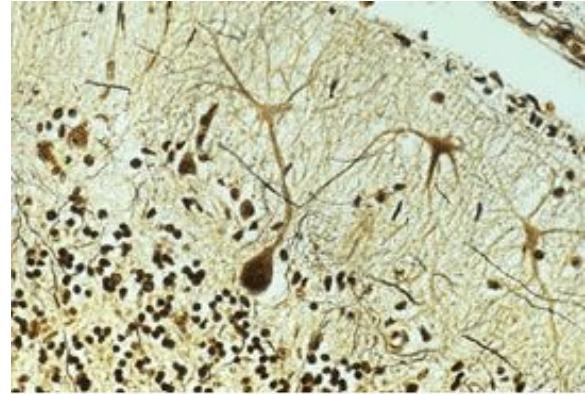
Menkes Syndrome

Menkes syndrome is an inborn error of metabolism that markedly decreases the cells' ability to absorb copper. The disorder causes severe cerebral degeneration and arterial changes, resulting in death in infancy. The disease can often be diagnosed by looking at a victim's hair, which appears to be both whitish and kinked when viewed under a microscope.

Menkes' disease is transmitted as an X-linked recessive trait. Sufferers can not transport copper, which is needed by enzymes involved in making bone, nerve and other structures. A number of other diseases, including type IX Ehlers-Danlos syndrome, may be the result of allelic mutations (i.e. mutations in the same gene, but having slightly different symptoms) and it is hoped that research into these diseases may prove useful in fighting Menkes' disease.

If administered within the first few months of life, copper histidinate appears to be effective in increasing the life expectancy of some patients. However, this treatment only increases life expectancy from three to thirteen years of age, so can only be con-

sidered a palliative. A similar condition to Menkes' disease exists in mice; working with these model organisms will help give insight into human copper transport mechanisms, so helping to develop effective treatments for Menkes' sufferers.



Abnormal Purkinje cell dendrites in the brain of a patient with Menkes disease. [Image credit: Kevin Roth and Robert Schmidt, Washington University, St. Louis, MO, USA.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=menkes] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=menkes&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4502321&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=menkes%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=menkes] online books section

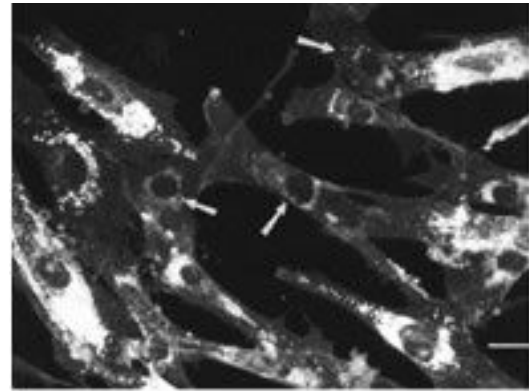
OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=309400] catalog of human genes and disorders

Niemann–Pick Disease

In 1914, German pediatrician Albert Niemann described a young child with brain and nervous system impairment. Later, in the 1920's, Luddwick Pick studied tissues after the death of such children and provided evidence of a new disorder, distinct from those storage disorders previously described.

Today, there are three separate diseases that carry the name Niemann–Pick: Type A is the acute infantile form, Type B is a less common, chronic, non-neurological form, while Type C is a biochemically and genetically distinct form of the disease. Recently, the major locus responsible for Niemann–Pick type C (NP-C) was cloned from chromosome 18, and found to be similar to proteins that play a role in cholesterol homeostasis.

Usually, cellular cholesterol is imported into lysosomes—'bags of enzymes' in the cell—for processing, after which it is released. Cells taken from NP-C patients have been shown to be defective in releasing cholesterol from lysosomes. This leads to an excessive build-up of cholesterol inside lysosomes, causing processing errors. NPC1 was found to have known sterol-sensing regions similar to those in other proteins, which suggests it plays a role in regulating cholesterol traffic.



Cells stained to show unesterified cholesterol in NP-C cells (white). The arrows show cell normalized by transfection with NPC1 DNA. [Reproduced with permission from Carstea et al. (1997) *Science* 277, 228-231.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=Niemann-Pick] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=Niemann-Pick&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557803&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=Niemann-Pick%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=Niemann-Pick] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=257200] catalog of human genes and disorders

Websites

Fact sheet [www.ninds.nih.gov/health_and_medical/disorders/niemann.doc.htm] from the National Institute of Neurological Disorders and Stroke, NIH

National Niemann-Pick Disease Foundation [www.nnpdf.org] an educational, support and fund-raising organization

Obesity

Obesity is an excess of body fat that frequently results in a significant impairment of health. Doctors generally agree that men with more than 25% body fat and women with more than 30% are obese. Obesity is a known risk factor for chronic diseases including heart disease, diabetes, high blood pressure, stroke and some forms of cancer. Evidence suggests that obesity has more than one cause: genetic, environmental, psychological and other factors may all play a part.

The hormone leptin, produced by adipocytes (fat cells), was discovered about three years ago in mice. Subsequently the human Ob gene was mapped to chromosome 7. Leptin is thought to act as a lipostat: as the amount of fat stored in adipocytes rises, leptin is released into the blood and signals to the brain that the body has enough to eat. However, most overweight people have high levels of leptin in their bloodstream, indicating that other molecules also effect feelings of satiety and contribute to the regulation of body weight.

The discovery of leptin has initiated a flurry of research into the molecular basis of weight control. A whole network of signals contributes to weight homeostasis, and other key players are being discovered on an ongoing basis. Mice have proved to be an extremely useful model for human obesity, and have helped to begin to unravel the compo-

nents that contribute to maintaining body weight. Since the market for effective weight-reducing therapies is enormous, drug companies are working alongside basic scientists to find possible drug targets among the tangle of molecules that control body weight.



A mouse with the Obese (Ob) mutation and a normal mouse. [Image credit: Jeff Friedman, Rockefeller University, New York, NY, USA. Reprinted from Science, with permission.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=obesity] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=obesity&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557715&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=obesity+gene%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=obesity] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=164160] catalog of human genes and disorders

Websites

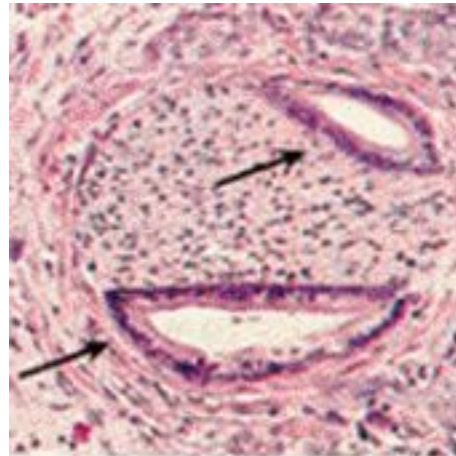
Weight-control information network [www.niddk.nih.gov/health/nutrit/win.htm] from the National Institute of Diabetes and Digestive and Kidney Diseases, NIH

Pancreatic Cancer

The pancreas is responsible for producing the hormone insulin, along with other substances. It also plays a key role in the digestion of protein. There were an estimated 27,000 new cases of pancreatic cancer in the US in 1997, with 28,100 deaths from the disease.

About 90% of human pancreatic carcinomas show a loss of part of chromosome 18. In 1996, a possible tumor suppressor gene, DPC4 (Smad4), was discovered from the section that is lost in pancreatic cancer, so may play a role in pancreatic cancer. There is a whole family of Smad proteins in vertebrates, all involved in signal transduction of transforming growth factor β (TGF β) related pathways. Other tumor suppressor genes include p53 and Rb, which, if mutated or absent from the genome can contribute to cancerous growth in a variety of tissues.

DPC4 (Smad4) homologs exist in the worm (*Caenorhabditis elegans*), mouse and the fly (*Drosophila*). In *Drosophila*, when the gene is not present, there a number of developmental defects. Likewise, homozygous Smad4 mutant mouse embryos die before embryonic day 7.5, and have reduced size because of reduced cell proliferation. Research on these model organisms should help elucidate the role of Smad4 and related proteins in humans.



Loss of DPC4 (Smad4) gene causes pancreatic cancers to grow aggressively, as seen by tumor cells invading a nerve bundle. [Image credit: R.H. Hruban, Johns Hopkins University, Baltimore, MD, USA. Reprinted from SCIENCE, with permission.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=pancreatic+cancer] see gene locations
 LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=pancreatic+cancer&ORG=Hs&V=0] collection of gene-related information
 Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4885457&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=pancreatic+cancer%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text
 Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=pancreatic+cancer] online books section
 OMIM [www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=PureSearch&db=omim&details_term=pancreatic%20cancer] catalog of human genes and disorders

Websites

CancerNet [cancernet.nci.nih.gov/] from the National Cancer Institute, NIH
 Oncolink [oncolink.upenn.edu/] comprehensive cancer information from the University of Pennsylvania
 American Cancer Society [www.cancer.org] research and patient support
 MEDLINEplus [www.nlm.nih.gov/medlineplus/pancreaticcancer.html] links on pancreatic cancer compiled by the National Library of Medicine

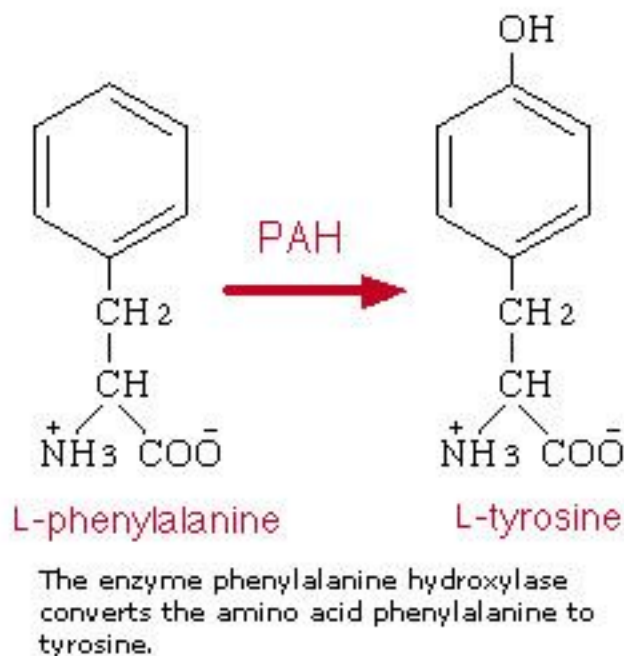
Phenylketonuria

Phenylketonuria (PKU) is an inherited error of metabolism caused by a deficiency in the enzyme phenylalanine hydroxylase. Loss of this enzyme results in mental retardation, organ damage, unusual posture and can, in cases of maternal PKU, severely compromise pregnancy.

Classical PKU is an autosomal recessive disorder, caused by mutations in both alleles of the gene for phenylalanine hydroxylase (PAH), found on chromosome 12. In the body, phenylalanine hydroxylase converts the amino acid phenylalanine to tyrosine, another amino acid. Mutations in both copies of the gene for PAH means that the enzyme is inactive or is less efficient, and the concentration of phenylalanine in the body can build up to toxic levels. In some cases, mutations in PAH will result in a phenotypically mild form of PKU called hyperphenylalanemia. Both diseases are the result of a variety of mutations in the PAH locus; in those cases where a patient is heterozygous for two mutations of PAH (ie each copy of the gene has a different mutation), the milder mutation will predominate.

A form of PKU has been discovered in mice, and these model organisms are helping us to better understand the disease, and find treatments against

it. With careful dietary supervision, children born with PKU can lead normal lives, and mothers who have the disease can produce healthy children.



Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=phenylketonuria] see gene locations
 LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=phenylketonuria&ORG=Hs&V=0] collection of gene-related information
 Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557819&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=phenylketonuria%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text
 Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=phenylketonuria] online books section
 OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=261600] catalog of human genes and disorders

Websites

National PKU News [www.pkunews.org] news and information about PKU
 GeneClinics [www.geneclinics.org/profiles/pku/] a medical genetics resource

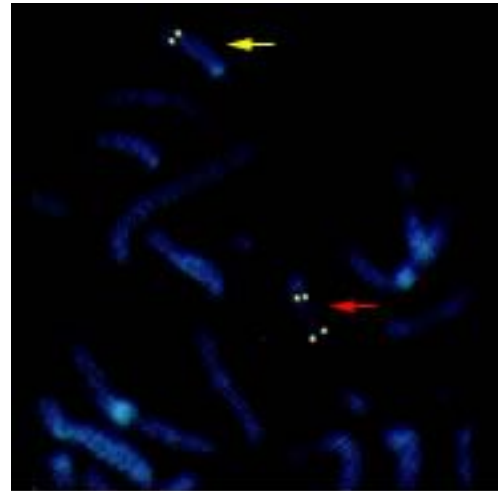
Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is an uncommon inherited disorder characterized by mental retardation, decreased muscle tone, short stature, emotional lability and an insatiable appetite which can lead to life-threatening obesity. The syndrome was first described in 1956 by Drs. Prader, Labhart, and Willi.

PWS is caused by the absence of segment 11-13 on the long arm of the paternally derived chromosome 15. In 70-80% of PWS cases, the region is missing due to a deletion. Certain genes in this region are normally suppressed on the maternal chromosome, so, for normal development to occur, they must be expressed on the paternal chromosome. When these paternally derived genes are absent or disrupted, the PWS phenotype results. When this same segment is missing from the maternally derived chromosome 15, a completely different disease, Angelman syndrome, arises. This pattern of inheritance — when expression of a gene depends on whether it is inherited from the mother or the father — is called genomic imprinting. The mechanism of imprinting is uncertain, but, it may involve DNA methylation.

Genes found in the PWS chromosomal region code for the small ribonucleoprotein N (SNRPN). SNRPN is involved in mRNA processing, an intermediate step between DNA transcription and protein formation. A mouse model of PWS has been developed with a large deletion which includes the SNRPN region and the PWS 'imprinting centre' (IC) and shows a phenotype similar to infants with PWS.

These and other molecular biology techniques may lead to a better understanding of PWS and the mechanisms of genomic imprinting.



In the Prader-Willi syndrome (PWS) cell above, the maternally derived chromosome 15 (red arrow) shows two signals: one from a control area (which is also seen in the paternally derived chromosome [yellow arrow]) and another, which is from the PWS region. This signal is missing from the paternal chromosome because the region is deleted in this PWS patient. [Reproduced with permission from Martin et al. (1998) *Am J Psychiatry* Sep; 155(9):1265-73.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=prader-willi] see gene locations
 LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=prader-willi&ORG=Hs&V=0] collection of gene-related information
 Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=14748674&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=prader-willi%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text
 Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=prader-willi] online books section
 OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=176270] catalog of human genes and disorders

Websites

Prader-Willi Syndrome Association (USA) [www.pwsausa.org/] information, education, and support services
 GeneClinics [www.geneclinics.org/profiles/pws/] a medical genetics resource

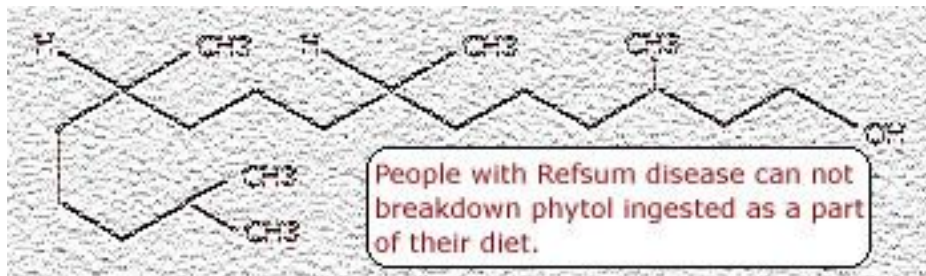
Refsum Disease

Refsum disease is a rare disorder of lipid metabolism that is inherited as a recessive trait. Symptoms may include a degenerative nerve disease (peripheral neuropathy), failure of muscle coordination (ataxia), retinitis pigmentosa (a progressive vision disorder), and bone and skin changes. Refsum disease is characterized by an accumulation of phytanic acid in the plasma and tissues. is a derivative of phytol, a component of chlorophyll.

In 1997 the gene for Refsum disease was identified and mapped to chromosome 10. The protein product of the gene, PAHX, is an enzyme that is

required for the metabolism of phytanic acid. Refsum disease patients have impaired PAHX - phytanic acid hydrolase. It is thought that Refsum disease is a peroxisomal disorder, since human PAHX contains PTS2 localization sequences, which target it to the peroxisome.

Our bodies can not synthesize phytanic acid: we have to obtain all of it from our food. Therefore, prolonged treatment with a diet deficient in phytanic acid can be beneficial.



Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=refsum] see gene locations
 LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=refsum&ORG=Hs&V=0] collection of gene-related information
 Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=5453884&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=refsum%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text
 Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=refsum] online books section
 OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=266500] catalog of human genes and disorders

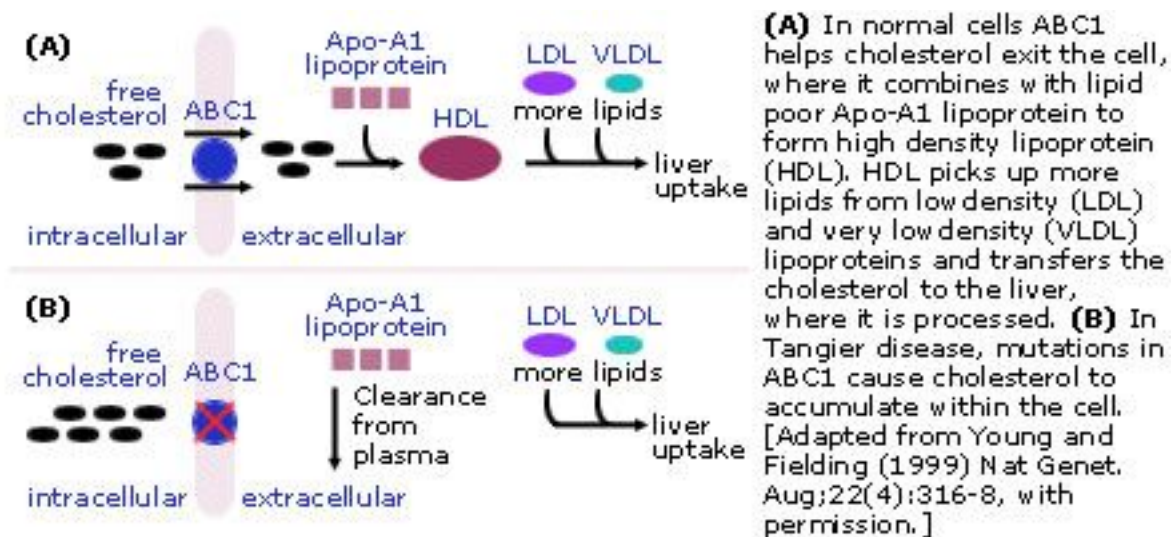
Tangier Disease

Tangier disease (TD) is a genetic disorder of cholesterol transport named for the secluded island of Tangier, located off the coast of Virginia. TD was first identified in a five-year-old inhabitant of the island who had characteristic orange tonsils, very low levels of high density lipoprotein (HDL) or 'good cholesterol', and an enlarged liver and spleen.

TD is caused by mutations in the *ABC1* (ATP-binding cassette) gene on chromosome 9q31. *ABC1* codes for a protein that helps rid cells of excess cholesterol. This cholesterol is then picked up by HDL particles in the blood and carried to the liver, which processes the cholesterol to be reused

in cells throughout the body. Individuals with TD are unable to eliminate cholesterol from cells, leading to its buildup in the tonsils and other organs.

The discovery of this important cholesterol transport gene may lead to a better understanding of the inverse relationship between HDL levels and coronary artery disease, an important killer in the US. New drugs that regulate HDL levels may be developed and such drugs would not only help individuals with TD, but also people with more common disorders such as familial HDL deficiency. This is a good illustration of how research into rare diseases can sometimes help more common disorders.



Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=Tangier%20OR%20ABCA1] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=Tangier&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=5915658&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=Tangier%20AND%2022pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=Tangier] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=205400] catalog of human genes and disorders

Websites

American Heart Association [amhrt.org] fighting heart disease and stroke

National Heart, Lung and Blood Institute, NIH [www.nhlbi.nih.gov/health/public/heart/] cardiovascular information

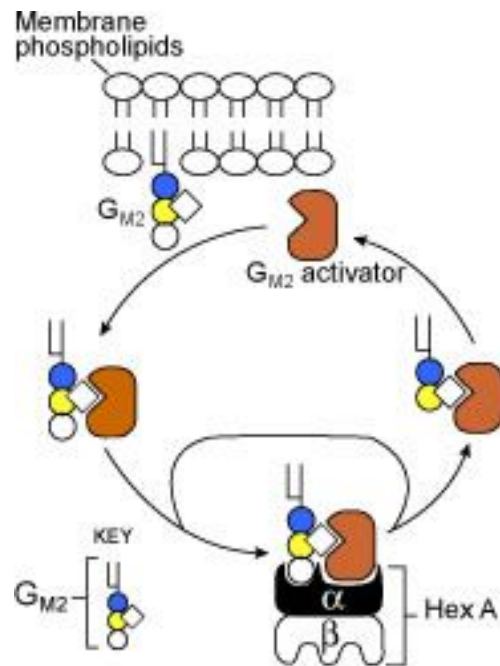
Tay-Sachs Disease

Tay-Sachs disease, a heritable metabolic disorder commonly associated with Ashkenazi Jews, has also been found in the French Canadians of South-eastern Quebec, the Cajuns of Southwest Louisiana, and other populations throughout the world. The severity of expression and the age at onset of Tay-Sachs varies from infantile and juvenile forms that exhibit paralysis, dementia, blindness and early death to a chronic adult form that exhibits neuron dysfunction and psychosis.

Tay-Sachs is an autosomal recessive disease caused by mutations in both alleles of a gene (*HEXA*) on chromosome 15. *HEXA* codes for the alpha subunit of the enzyme β -hexosaminidase A. This enzyme is found in lysosomes, organelles that break down large molecules for recycling by the cell. Normally, β -hexosaminidase A helps to degrade a lipid called GM2 ganglioside, but in Tay-Sachs individuals, the enzyme is absent or present only in very reduced amounts, allowing excessive accumulation of the GM2 ganglioside in neurons. The progressive neurodegeneration seen in the varied forms of Tay-Sachs depends upon the speed and degree of GM2 ganglioside accumulation, which in turn is dependent upon the level of functional β -hexosaminidase A present in the body.

A mouse model has been developed for Tay-Sachs, although its usefulness is limited since Tay-Sachs mice possess a minor alternative pathway for breaking down GM2 ganglioside. Treatment of the late onset form of Tay-Sachs with a ganglioside synthesis inhibitor shows promise. The effectiveness of this and other treatments on individuals with the infantile (the most common) form of the disease is extremely limited since the extent of neurological damage prior to birth is unknown. The difficulty in reversing such damage will make it hard to develop an effective treatment for the infantile form of the disease. It is hoped, however, that the latter onset forms of Tay-Sachs may prove responsive to treat-

ment, and such treatment combined with the DNA and enzymatic screening programs currently in use will lead to the eventual control of this disease.



Model for G_{M2} ganglioside metabolism. Under normal conditions, β -hexosaminidase works in the lysosome of nerve cells to breakdown unwanted ganglioside G_{M2}, a component of the nerve cell membrane. This requires three components: an α -subunit, a β -subunit and an activator subunit. In Tay Sachs disease, the alpha subunit of hexosaminidase malfunctions, leading to a toxic build-up of the G_{M2} ganglioside in the lysosome. [Adapted from: Chavany, C. and Jendoubi, M. (1998) *Mol. Med. Today*, 4: 158-165, with permission.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=Tay-Sachs%20OR%20HEXA] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=Tay-Sachs&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4504371&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=Tay-Sachs%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=Tay-Sachs] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=272800] catalog of human genes and disorders

Websites

Genes and Disease

Nutritional and Metabolic Diseases

Fact Sheet [www.ninds.nih.gov/health_and_medical/disorders/taysachs_doc.htm] from National Institute of Neurological Disorders and Stroke

NTSAD [www.ntsad.org/] National Tay-Sachs and Allied Diseases Association

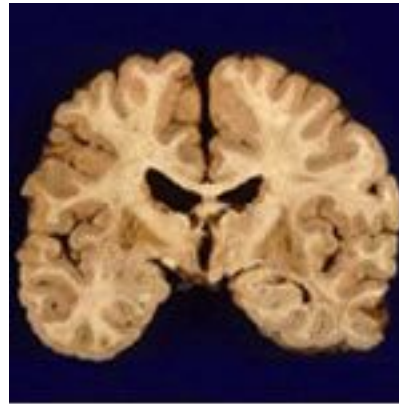
GeneClinics [www.geneclinics.org/profiles/tay-sachs/] a medical genetics resource

Wilson's Disease

Wilson's Disease is a rare autosomal recessive disorder of copper transport, resulting in copper accumulation and toxicity to the liver and brain. Liver disease is the most common symptom in children; neurological disease is most common in young adults. The cornea of the eye can also be affected: the 'Kayser-Fleischer ring' is a deep copper-colored ring at the periphery of the cornea, and is thought to represent copper deposits.

The gene for Wilson's disease (ATP7B) was mapped to chromosome 13. The sequence of the gene was found to be similar to sections of the gene defective in Menkes disease, another disease caused by defects in copper transport. The similar sequences code for copper-binding regions, which are part of a transmembrane pump called a P-type ATPase that is very similar to the Menkes disease protein.

A homolog to the human ATP7B gene has been mapped to mouse chromosome 8, and an authentic model of the human disease in rat is also available (called the Long-Evans Cinnamon [LEC] rat). These systems will be useful for studying copper transport and liver pathophysiology, and should help in the development of a therapy for Wilson disease.



In Wilson's disease, toxic levels of copper accumulate and damage many tissues and organs, including the basal ganglia of the brain. [Image credit: Kevin Roth and Robert Schmidt, Washington University, St. Louis, MO, USA.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=ATP7B] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=ATP7B&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4502323&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=ATP7B%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=ATP7B] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=277900] catalog of human genes and disorders

Websites

Fact sheet [www.ninds.nih.gov/health_and_medical/disorders/wilsons_doc.htm] from the National Institute of Neurological Disorders and Stroke, NIH

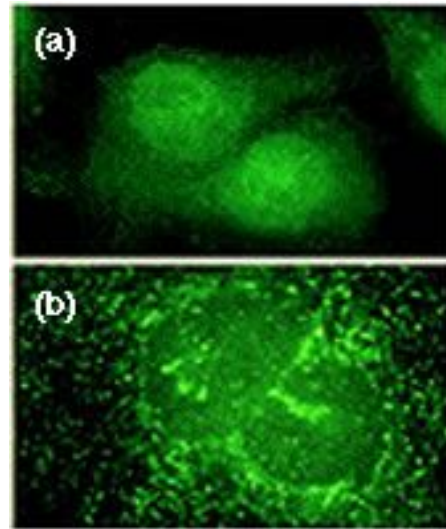
GeneClinics [www.geneclinics.org/profiles/wilson/] a medical genetics resource

Zellweger Syndrome

Zellweger syndrome is a rare hereditary disorder affecting infants, and usually results in death. Unusual problems in prenatal development, an enlarged liver, high levels of iron and copper in the blood, and vision disturbances are among the major manifestations of Zellweger syndrome.

The PXR1 gene has been mapped to chromosome 12; mutations in this gene cause Zellweger syndrome. The PXR1 gene product is a receptor found on the surface of peroxisomes - microbodies found in animal cells, especially liver, kidney and brain cells. The function of peroxisomes is not fully understood, although the enzymes they contain carry out a number of metabolically important reactions. The PXR1 receptor is vital for the import of these enzymes into the peroxisomes: without it functioning properly, the peroxisomes can not use the enzymes to carry out their important functions, such as cellular lipid metabolism and metabolic oxidations.

There is a yeast homolog to human PXR1, which should allow powerful molecular genetic techniques to be used in the investigation of the normal role of peroxisomes in cells, as well as the molecular events that occur in disease states.



Peroxisomes are not detected in Zellweger syndrome fibroblasts (a), but can be reconstituted by transfection with PXR1 gene (b). [Image credit: Nancy Braverman, Gabrielle Dodt, Hugo Moser, Stephen Gould and David Valle, Johns Hopkins University, Baltimore, MD, USA.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=zellweger] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=zellweger&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4506347&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=zellweger%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=zellweger] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=600414] catalog of human genes and disorders

Websites

Fact sheet [www.ninds.nih.gov/health_and_medical/disorders/zellwege_doc.htm] from the National Institute of Neurological Disorders and Stroke, NIH